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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/043,665	10/05/98	RUSSELL S	MEWB112010

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/043,665	RUSSELL ET AL.	
	Examiner	Art Unit	
	Ram Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,11 and 12* is/are pending in the application.

4a) Of the above claim(s) *13-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 ,11 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☒ Interview Summary (PTO-413) Paper No(s). *22* .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. The finality of the previous office action of 9-19-2000 is withdrawn in view of the newly discovered reference(s) and new grounds of rejections.

2. Amendment filed 3-19-01 has been entered.

3. Claims 9 and 10 have been canceled.

4. Claims 13-21 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 10, filed 11-15-99.

5. Claims 1-8, 11 and 12 are under instant consideration.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-8, 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an in vitro method of transforming a population of quiescent hematopoietic stem cells with a nucleic acid encoding a polypeptide for treating a disease or disorder, the method comprising: exposing the quiescent hematopoietic stem cells to a retroviral packaging cell wherein the packaging cell produces a retroviral particle comprising a nucleic acid encoding the polynucleotide for treating a disease or disorder and wherein the packaging cell expresses a nucleic acid encoding a growth factor so that the growth factor is displayed on the surface of the packaging cell and wherein the growth factor displayed on the surface of the packaging cells induces quiescent hematopoietic stem cells to divide, and the quiescent hematopoietic stem cells are infected by the retroviral particle so that the nucleic acid encoding the polypeptide for treatment is incorporated into the genome of the quiescent hematopoietic stem cells, does not reasonably provide enablement for the claimed method wherein the hematopoietic stem cells are exposed to the retroviral packaging cells in vivo or a method wherein any and all quiescent cells are exposed to retroviral packaging cells in vivo or in vitro. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to making and practicing the invention commensurate in scope with these claims.

Additionally, while the specification enables claims 11 and 12 for a method of treating a patient wherein the method comprises the steps of: transforming a population of autologous quiescent hematopoietic stem cells in vitro with a nucleic acid encoding a polypeptide for treating a disease or disorder, the method comprising: exposing the quiescent hematopoietic stem cells to a retroviral packaging cell wherein the packaging cell produces a retroviral particle comprising a nucleic acid encoding the polynucleotide for treating a disease or disorder and wherein the packaging cell expresses a nucleic acid encoding a growth factor so that the growth factor is displayed on the surface of the packaging cell and wherein the growth factor displayed on the surface of the packaging cells induces quiescent hematopoietic stem cells to divide, and the quiescent hematopoietic stem cells are infected by the retroviral particle so that the nucleic acid encoding the polypeptide for treatment is incorporated into the genome of the quiescent hematopoietic stem cells, the specification does not reasonably provide enablement for practicing the claimed method wherein any and all quiescent cells are transformed by the method.

It is noted that claim 1 recites the transformation of quiescent cells with a nucleic acid encoding a protein for treatment by exposing the quiescent cells to a cell line of retroviral packaging cells which comprise the nucleic acid encoding the therapeutic protein and which express a growth factor that induces the quiescent cells to divide which results in the infection of the cell by the retroviral particle and the nucleic acid encoding the therapeutic protein gets incorporated into the genome of the dividing cells. When given its broadest interpretation, the claimed method would encompass an in vivo method and also transformation of any and all quiescent cells that can be used in ex vivo treatment method and such cells could encompass allogeneic, xenogeneic as well as autologous cellsThe specification in examples 1-4 (pages 14-25) discloses method of making retroviral vectors, retrovirus producer cells, packaging cells, infection of cells (progenitor cells from umbilical cord blood and hematopoietic stem cells), characterization of such cells and the proteins produced by these cells by immunoblotting and targeting of cells using said vectors. However, the specification fails to provide any guidance, working example or evidence as to whether the method can be used for transforming any and all quiescent cells, such as senescent cells or non-hematopoietic quiescent cells, or whether the claimed method can be used for transforming quiescent cells in vivo, as discussed below.

The specification on page 5, lines defines quiescent cells as cells that are unlikely to enter mitosis within the next 24 hours in the absence of appropriate growth stimulus and could include stem cells of hematopoietic as well as non-hematopoietic tissues, resting T and B cells, germ cells etc. However, from the teachings of the specification it is not clear whether the method can be used for transforming any and all quiescent cells, such as senescent cells because the requirement of growth factors for different cell types is different and some cells may require more than one growth factors for entering into a new cycle of mitosis. In case of senescent cells, it is not clear whether senescent cells can always be activated to start dividing. For example, Phillips et al (Journal of Cellular Physiology 151:206-212, 1992) disclosed that senescent cells selected with BrdU could not respond to growth factor stimulation of c-fos to start mitosis again. Likewise these authors noted that senescent cells that had already completed their 100% of their proliferative life span could also not be induced with c-fos to go into mitosis. Therefore, at the time of the invention, it was unpredictable whether any and all quiescent cells, for example, senescent cells could be induced to undergo cell division by a growth factor. The specification does not provide any guidance as to how an artisan of skill would have activated cells that were not responsive to a growth factor or how to activate cells that have completed their proliferative life scan.

In addition to senescent cells, different cells may require a combination of growth factors for activation to enter mitosis again. For example, Maurice et al (Blood 94:401-410, 1999; an article in which the inventor is a co-author), four years after the priority date of the claimed invention noted that display of IL-2 on vector particles may not be sufficient to give highly efficient transduction of primary T cells because such cells would need preactivation by another antigen. Likewise, in airway epithelial cells need prestimulation with keratinocyte growth factor (see discussion on page 408, column 1). Additionally, Maurice et al noted that several aspects of their study pointed to the need for improvements to optimize the strategy for clinical gene transfer (see last paragraph in column 1 on page 408). For example, IL-2 displayed on retroviral particles did not activate the IL-2 dependent cells, rather the activation occurred due to IL-2-SU envelope shed form the vector particles. While the claimed method does not recite using vector particles displaying growth factor, such a condition of shedding growth factor in the culture medium would occur more. This also represents an unpredictability of the claimed method, as to whether the method can be practiced with any and all cells. The specification

does not provide any guidance as to how an artisan of skill have activated any and all quiescent cells by the claimed method in light of the unpredictability issues discussed above.

Next, it is noted that the claimed method would encompass the method to be practiced in vivo, however, the specification does not teach as to how the method would have been carried out in vivo. For example, the specification fails to teach what would be the consequence of administering retroviral packaging cells to a mammal or a patient. The specification does not teach whether cells were to be administered by systemic methods or locally to a certain tissue. In any case, such an administration would have resulted in contacting all the cells of the particular tissue or of the entire mammal or patient and if transfer of the retroviral vector was incorporated in cells of the host, there would be indiscriminated expression of the recombinant protein in every cell type and every tissue , if retroviral vector was expressed and the specification does not teach what will be the consequence of such indiscriminated expression of a protein. Alternatively, if the packaging cells were administered to a certain tissue, it would result in infection of all the cell types of the tissue, and again the specification does not teach what would be the consequence of the method. Claimed methods as instantly recited would also encompass a retroviral packaging cell line carrying any and all vector, however, the specification is only enabling for a packaging cell which carries a retroviral vector. For example, while a retroviral packaging cell would produce retroviral particles that would infect the target cell, how would a plasmid or another vector be produced by the packaging cell. It is noted that neither the specification nor the prior art, at the time of the invention, taught that a retroviral packaging cell line that carries a plasmid or any vector other than retroviral vector comprising a therapeutic gene would be able to transduce a target cell with the vector.

Regarding the method treatment, it is noted that the limitation of the method pertaining to transforming any and all quiescent cells would be the same as discussed above. In addition to these limitations there will be the limitation of the immunological tolerance due to the allogeneic or xenogeneic cells. It is well known in the art that one major problem of cell transplantation is rejection of the transplanted cells by the host (see first two paragraphs on page 54 of Kohn DB. Clin. Exp. Immunol. 107:54-57, 1997). As Kohn et al noted even when bone marrow from HLA-identical sibling is used, there is 25-35% chance of mild to moderate graft-versus-host disease from donor derived T lymphocytes responding to recipient antigens. Therefore, the specification fails to teach how can xenogeneic or allogeneic cells could be used. Since, claims do not recite whether the cells being used for administration and transplantation are xenogeneic, allogeneic

or autologous, while autologous cells may be more predictable to use for treatment, the immunological implications of the administration of said cells or what would have been the rejection rate in the patients could not be predicted. Furthermore, the method will be complicated by the effect of the growth factor or other protein to be produced in the cell because the growth factor may result in activation of the T cells of the patient resulting in a more severe graft-versus-host disease. The specification does not provide any guidance as to how an artisan would addressed the issue of rejection of the cells when xenogeneic or allogeneic cells were used in treatment.

Accordingly, limitation of the scope of the claimed invention to an in vitro method of transforming a population of quiescent hematopoietic stem cells with a nucleic acid encoding a polypeptide for treating a disease or disorder, the method comprising: exposing the quiescent hematopoietic stem cells to a retroviral packaging cell wherein the packaging cell produces a retroviral particle comprising a nucleic acid encoding the polynucleotide for treating a disease or disorder and wherein the packaging cell expresses a nucleic acid encoding a growth factor so that the growth factor is displayed on the surface of the packaging cell and wherein the growth factor displayed on the surface of the packaging cells induces quiescent hematopoietic stem cells to divide, and the quiescent hematopoietic stem cells are infected by the retroviral particle so that the nucleic acid encoding the polypeptide for treatment is incorporated into the genome of the quiescent hematopoietic stem cells, is proper.

Response to Arguments

Applicant's arguments filed 9-19-00 have been fully considered but they are not persuasive.

It is noted that the full enablement rejection of claims 11 and 12 has been changed to a scope rejection in response to the amendment and Applicant's argument. In response to Applicants arguments regarding strategies of cellular transplantation and for reducing immunoreactivity, Applicant's citation of the various references is acknowledged. However, it is noted that none of these references talks about xenogeneic or allogeneic transplantation and that matching of the donor and recipient organs is required before transplantation of an organ is carried out. As has been noted in the previous office action, neither the specification nor the prior art provides sufficient guidance for practicing the claimed invention in the context of treating a patient with xenogeneic cell transplantation. Applicants have attached 12 review

articles related to transplantation, however, they have not cited what sections of these articles are relevant to the issue at hand. While these articles provide review of the art of transplantation, at the time of invention, it was not routine to carry out xenogeneic transplantation for treatments. Furthermore, Applicant's attention is drawn to a review on transplantation in 1998, three years after the priority date of the claimed invention, by Lambrights et al (Transplantation 66:547-561, 1998). Lambrights et al, in their review, provide a table of discordant organ xenotransplantation in human recipients (see table 1 on page 548) which shows that the survival of xeno-organs in humans has been less than 72 hours. This very clearly reflects the state of the art of xenotransplantation even three years after the time of the instant invention was unpredictable. Even when grafts have been carried out in primates (pig to primate), survival of the graft has been in hours or some time in days (see tables 2-7). Finally, Lambrights et al conclude, "on the basis of the results of discordant organ....., we can conclude that some progress is made...., we have some way to go before further clinical trials can be justified" (see second paragraph in column 1 on page 556). In summary, the state of xenotransplantation was unpredictable at the time of the invention and the Applicants arguments and cited references are not sufficient to obviate rejections relating to a method of treatment with xenogeneic and allogeneic cells.

Since the full enablement rejection of claims 11 and 12 has been changed to scope rejection, Applicants arguments are moot regarding other issues of enablement.

Response to Amendment

The declaration of Colin M. Casimir under 37 CFR 1.132 filed 3-19-01 has been entered. It is noted that the declaration is sufficient to overcome the rejection of claims 11 and 12 of treatment and in response the total rejection has been changed to a scope rejection. However, the declaration is not sufficient to obviate the new grounds of rejection as set forth above because it does not discuss these issues.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

9. Claims 1-8 and 11-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 11 recite the phrase "the growth factor displayed on the surface of the cell line" or "the cell line carrying." However it is not clear as to how a cell line can display on its surface because the cell has a surface not a cell line which is collection of cells. Recitation of "the growth factor displayed on the surface of the retroviral packaging cell" will be remedial. Use of the phrase "a retroviral packaging cell" in place of "a retroviral packaging cell line" in line 3 of claim 1 and line 2 of claim 11 is also suggested.

The antecedent basis for "the cells" is not clear in claims 1 and 11 because the claim recites a quiescent cell. Recitation of "the quiescent cells" is suggested.

Claims 5 recites the limitations "a viral envelope protein" in line 2 and "a retroviral envelope protein" in line 3, however it is not clear whether the two terms are related and are supposed to mean same term or different terms.

Claim 7 recites the limitation "the envelope protein" in line 2. There is insufficient antecedent basis for this limitation in the claim because the independent claim, claim 1, does not recite an envelope protein.

Claim 11 recites the limitation "the surface bound growth factor" in line 7. There is insufficient antecedent basis for this limitation in the claim because a surface bound growth factor is not recited in the claim before.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-4, and 11-12 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Luskey et al (Blood 80:3960402, 1992).

Claim 1 recites method of transforming a population of quiescent cells using a retroviral packaging cell line that expresses a growth factor encoding nucleic acid or retroviral particles

that express a fusion of viral envelope protein with a growth factor so that the growth factor is displayed on the surface of the cell line or the viral particle and wherein the binding of the growth factor induces target cells to divide and the nucleic acid encoding the growth factor is incorporated into the genome of the cells. Dependent claims limit the quiescent cells to hematopoietic stem cells.

Luskey et al teach that prestimulation of bone marrow with various cytokines including stem cell factor increases the retroviral-mediated gene transfer (human ADA encoding cDNA) into murine hematopoietic stem cells (HSC) (see the abstract and also materials and methods section). Bone marrow cells were stimulated with growth factors and prestimulated cells were cocultured with producer cells. Afterwards, non-adherent cells from the coculture were injected into syngeneic recipient mice. Luskey et al also teach that transformed cells when administered to mice show expression of hADA into the peripheral blood and that prestimulation with cytokines and growth factors results into higher levels of hADA expression in mice (see last paragraph in column 2 on page 398 continued on page 399, column 1). Luskey et al further discusses that the hematopoietic microenvironment may play an important role in the maintenance of reconstituting HSC. Additionally, they note that there is a significant role for the presentation of steel factor or stem cell factor in the context of the microenvironment and that stromal cells (producer cells) express both membrane-bound and secreted SCF, although the level or protein expression is low (see first full paragraph in column 2 on page 401). They conclude that use of the recombinant SCF during prestimulation of the target HSC improves gene transfer efficiency into a primitive stem cell population and may be useful in the further application of gene transfer methods into the HSC of larger animal species, where the efficiency of gene transfer into long-lived stem cells is still problematic(last sentence in the last paragraph in column 2 on page 401). Regarding claims 3 and 4, it is noted that stromal cells express their endogenous growth factors on their surface, for example, stem cell factor (see first full paragraph in column 2 on page 401).

Accordingly, the method of claims 1-4 is anticipated by Luskey et al. Regarding claims 11 and 12, it is noted that the art by Luskey et al teaches the method steps and expression of ADA in mice therefore, it anticipates the invention of claims 11 and 12.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1, and 5-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Luskey et al (Blood 80:3960402, 1992) in view of Paul et al (US 5,736,387, 4-7-1998, effective filing date 6-1-94).

Claim 1 recites method of transforming a population of quiescent cells using a retroviral packaging cell line that expresses a growth factor encoding nucleic acid or retroviral particles that express a fusion of viral envelope protein with a growth factor so that the growth factor is displayed on the surface of the cell line or the viral particle and wherein the binding of the growth factor induces target cells to divide and the nucleic acid encoding the growth factor is incorporated into the genome of the cells. Dependent claims limit the quiescent cells to hematopoietic stem cells. Claim 9 recites a population of cells produced by the method of claim 1 and cells comprise a nucleic acid that encodes a polypeptide for treating a disease or disorder.

Luskey et al teach that prestimulation of bone marrow with various cytokines including stem cell factor increases the retroviral-mediated gene transfer (human ADA encoding cDNA) into murine hematopoietic stem cells (HSC) (see the abstract and also materials and methods section). Bone marrow cells were stimulated with growth factors and prestimulated cells were cocultured with producer cells. Afterwards, non-adherent cells from the coculture were injected into syngeneic recipient mice. Luskey et al also teach that transformed cells when administered to mice show expression of hADA into the peripheral blood and that prestimulation with cytokines and growth factors results into higher levels of hADA expression in mice (see last paragraph in column 2 on page 398 continued on page 399, column 1). Luskey et al further discusses that the hematopoietic microenvironment may play an important role in the maintenance of reconstituting HSC. Additionally, they note that there is a significant role for the presentation of steel factor or stem cell factor in the context of the microenvironment and that stromal cells (producer cells) express both membrane-bound and secreted SCF, although the

level or protein expression is low (see first full paragraph in column 2 on page 401). They conclude that use of the recombinant SCF during prestimulation of the target HSC improves gene transfer efficiency into a primitive stem cell population and may be useful in the further application of gene transfer methods into the HSC of larger animal species, where the efficiency of gene transfer into long-lived stem cells is still problematic(last sentence in the last paragraph in column 2 on page 401). Luskey et al does not teach a fusion protein of the growth factor with a viral envelope protein wherein the growth factor is attached to the N-terminus of the retrovial envelope protein.

Paul et al teaches envelope fusion vectors that can be used in gene delivery. The vectors comprise chimeric targeting proteins that specifically alter the host range of the vector and the chimeric or fusion protein contains a ligand moiety that binds to receptors present on target cells and an uptake moiety that is capable of promoting the entry of the vector into the target cell. The ligand moiety is a cytokine that acts upon target cells and the uptake moiety is derived from a retroviral envelope protein (see abstract). Paul et al teach a vectors wherein IL-2 encoding sequences are fused at the N-terminal of envelope sequences of amphotropic murine retrovirus or of ecotropic murine virus (see figures 2 and 4 and examples 1 and 6). They also teach packaging cells that are transfected with said vector and retroviral particles produced by these cells (see examples 2,3 and 6, also see claims). Paul et al also teaches that the fusion protein of their invention can be used to modulate the targeted cells in accordance with the activity of the cognate cytokine (cytokine fusion partner of the growth factor-envelope fusion protein). They further assert that fusion protein will provide a combination of activities, such as, binding to specific target cells, delivery of the vector nucleic acid into the cell and cytokine modulation of the cells targeted. Such activities will be advantageous for in vivo gene delivery where it may be otherwise problematic or impossible to induce the targeted cells to divide and thus promote stable incorporation of the transferred gene (see lines 8-32 in column 15). Paul et al further assert that ligand moieties derived from flk2 ligand, that is specifically expressed on early hematopoietic cells or stem cells, can also be expressed as fusion protein of their invention and such a fusion protein could be used to direct infection to lymphohematopoietic progenitor cells (see lines 56-67 of column 15 continued in lines 1-7 of column 6).

Accordingly, at the time of the invention, it would have been obvious to one of ordinary skill in the art to transform the producer cells of Luskey et al with the envelope fusion vector of Paul et al so that the producer cells express the envelope growth factor because it would have

allowed an increased number of the growth factor on the membrane of the producer cells, which in turn would have facilitated the efficiency of the infection of HSC by the retroviral vector produced by the producer cells and then use these producer cells to transform hematopoietic stem cells, and use the hematopoietic cells in treatment of diseases, such as ADA deficiency (see the last paragraph in column 2 on page 401). An artisan would have been motivated to express the fusion protein on the membrane of the producer cells because the producer cells have low concentration of the endogenous growth factor such as the steel cell factor and because presentation of the stem cell factor on the membrane would have provided a better presentation of the stem cell factor in context of the producer cell microenvironment and hematopoiesis and also because the fusion protein will provide a combination of activities, such as, binding to specific target cells, delivery of the vector nucleic acid into the cell and cytokine modulation of the cells targeted (see the first full paragraph in column 2 on page 401). Such activities will be advantageous for in vivo gene delivery where it may be otherwise problematic or impossible to induce the targeted cells to divide and thus promote stable incorporation of the transferred gene (see lines 8-32 in column 15 in Paul et al). Furthermore, this would have eliminated the step of prestimulation of the HSC with the steel factor and cytokines before coculture with the producer cells.

Regarding claim 6, it is noted that fusion protein constructs with a cleavable linker between two polypeptides were known in the prior art for other purposes. But the presence of absence of the cleavable linker is not relevant for the use of the instantly claimed method.

14. Claim 3 rejected under 35 U.S.C. 103(a) as being unpatentable over Luskey et al (Blood 80:3960402, 1992) and Paul et al (US 5,736,387, 4-7-1998, effective filing date 6-1-94) as applied to claims 1,2, 4-5, and 7- 8 above, and further in view of Lyman et al (US 5,554,512, 9-10-1996, effective filing date 5-24-93).

Claim 3 limits the growth factor in the fusion protein of claim 1 to stem cell factor or flt3 ligand.

Teachings of Luskey et al and Paul et al have been summarized above. None of these prior arts teaches that the growth factor in the fusion protein is stem cell factor or flt3 ligand.

Lyman et al teaches ligands for flt3 receptors that can induce the growth, proliferation and differentiation of progenitor cells and stem cells. They also teach DNA encoding flt3 ligand, host cells transfected with cDNAs encoding flt3 ligands, methods improving gene transfer to a mammal using flt3 ligand and methods of improving transplantation using flt3 ligand. They

further assert that flt3 ligand can be used in treating patients with anemia, AIDS and various cancers (see abstract). Lyman et al assert that flt3 ligand of their invention can be used to increase or mobilize the number of circulating peripheral blood progenitor or stem cells, flt3 ligand can be administered to the patient or cells isolated from a patient can be treated with it ex vivo and flt3 ligand can be administered to a patient following transplantation of the isolated stem cells to facilitate engraftation thereof (see lines 49-67 in column 3). Lyman et al further assert that a cDNA encoding flt3 ligand may be transfected into cells to ultimately deliver its gene product to the targeted cell or tissue (see lines 18-24 in column 4).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to modify the retroviral vector of Paul et al (that encodes a fusion protein of a cytokine and retroviral envelope protein) by cloning the flt3 ligand cDNA taught by Lyman et al, transfect the vector in cells to make packaging cells that would produce retroviral particles that can infect stem cells and affect their proliferation due to the expression of flt3 ligand and use these cells for transforming hematopoietic stem cells in the method of Luskey et al with a reasonable expectation of success. As noted in paragraph 13, An artisan would have been motivated to express the fusion protein on the membrane of the producer cells because the higher expression of growth factors such as the flt3 would have provided a better presentation of the growth factor in context of the producer cell microenvironment and hematopoiesis.

15. No claim is allowed.

Applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c). For instruction, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608.

The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Kay Pinkney whose telephone number is (703) 305-3553.

Ram R. Shukla, Ph.D.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER